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Dysfunctions of Neuronal and Glial Cells in Schizophrenia with Emphasis on Their Communication

Narušení funkce neuronů a gliových buněk u schizofrenie s důrazem na jejich komunikaci

Bachelor's thesis

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Prohlášení
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Podpis

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Abstract

Schizophrenia is a serious neuropsychiatric disorder with prevalence in a population of 1 %. The brain is a highly complex system consisting of neurons and glia cells, which intensively communicate along themselves. The function of individual brain cells as well as their populations and their reciprocal communication can be disrupted under the certain environmental and genetic circumstances. At first, neuropsychiatric researches at the physiological level confirmed the dysfunction of neurons in schizophrenia and afterwards, also of the glia cells. This thesis maps knowledge rising especially from animal models of an abnormal function of neurons and individual types of glia, but also of their reciprocal physiological communication. In particular chapters, the physiological mechanisms of this communication and its dysfunction correlating with the presence of schizophrenic behavioral symptoms, is outlined. For the clarification, there are also introduced experimental models used in practice for the purpose of studying individual cell-specific dysfunctions.

Keywords: schizophrenia, neuron-glia communication, neuron, interneuron, glia, astrocyte, oligodendrocyte, microglia

Abstrakt

Schizofrenie je závažné neuropsychiatrické onemocnění, jehož prevalence v populaci je asi 1 %. Mozek je vysoce komplexní systém sestávající z neuronů a gliových buněk, které spolu navzájem intenzivně komunikují. Díky enviromentálním a genetickým vlivům může dojít k narušení funkce jednotlivých buněk, jejich populací a jejich vzájemné komunikace. Neuropsychiatrické výzkumy na fyziologické úrovni zprvu potvrdily neuronovou a později i gliovou dysfunkci u schizofrenie. Tato práce mapuje poznatky ze studií zejména animálních modelů abnormální funkce neuronů a jednotlivých typů gliových buněk, ale i jejich vzájemné fyziologické komunikace. V jednotlivých kapitolách jsou nastíněny fyziologické mechanismy této komunikace, jejichž dysfunkce koreluje s výskytem behaviorálních symptomů u schizofrenie. Pro přehlednost jsou uvedeny i experimentální modely, které se v praxi používají k výzkumu jednotlivých buněčně-specifických dysfunkcí.

Klíčová slova: schizofrenie, neuron-glie komunikace, neuron, interneuron, glie, astrocyt, oligodendrocyt, mikroglie

List of Abbreviations

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDNF: brain-derived neurotrophic factor
CA4: cornu ammonis area 4
CNS: central nervous system
C-PK11195: isoquinoline carboxamide
C1q: complement component
DA: dopamine
DAB: 1-4-dideoxy-1,4-imino-D-arabinitol
DLPFC: dorsolateral prefrontal cortex
DTI: diffusion tensor imaging
D1R: dopamine 1 receptor
D2R: dopamine 2 receptor
ECM: extracellular matrix
EGF: epidermal growth factor
erbB4: receptor tyrosine-protein kinase 4
GABA: γ-aminobutyric acid
GJ: gap junction
IL-1α, β: interleukin-1 α, β
KMO: kynurenine-3-monooxygenase
KYNA: kynurenic acid
L-AA: L-α-aminoadipate
LPS: lipopolysaccharide
MAM: methylazoxymethanol
MBP: myelin basic protein
MCT 1, 4: monocarboxylate transporter 1, 4
MRI: magnetic resonance imaging
mRNA: messenger RNA
NMDA: N-methyl-D-aspartate
NRG1: neuregulin-1
NVHL: neonatal ventral hippocampal lesion
OLIG 1, 2: oligodendrocyte growth factor 1,2
OPCs: oligodendrocyte-precursos-cells
PET: positron emission tomography
PFC: prefrontal cortex
plp1: proteolipid protein 1
PNS: peripheral nervous system
Poly I:C: polyinosinic-polycitidilic acid
PVI: parvalbumin
RNS: reactive nitrogen species
ROS: reactive oxygen species
SPECT: Single-photon emission computed tomography
TeNT: tetanus toxin
TLR3: toll-like receptor 3
TNF: tumor necrosis factor
TTX: tetrodotoxin
VTA: venral tegmental area
WM: working memory
α-ScTX: α-scorpion toxin

Outline

Introduction to Schizophrenia

In the past five decades, there has been plenty of hypotheses formulated explaining what, regarding the neuropsychiatric biology, stands behind the status of having a severe mental disorder such as schizophrenia. Most of them consider schizophrenia as a neurodevelopmental as well as debiliating disorder which manifests itself through many complex symptoms divided into three groups comprising positive (e.g. delusions and hallucinations), negative (e.g. emotional and social dysfunction) and cognitive (e.g. impairment in working memory and cognitive flexibility) symptoms. However, pharmacological treatment seems to be only effective relating to limited group of symptoms including the positive ones, whilst the negative and cognitive remain to be the core burden of patients everyday life.

Along the advancement of imaging technics such as MRI or PET, it is hypothesized that brains of schizophrenics are characterized by reorganization of network topology leading to an altered communication within and between brain regions resulting in the disturbance in the integration of information processing. Hence, researchers who are considering the projection of this disorder as an altered connectome aim at describing distinct spatiotemporal organizations that generate brain functions (Senden *et al.*, 2014; Cheng *et al.*, 2015; Collin *et al.*, 2017; Gollo, Roberts and Cocchi, 2017).

Most affected are cortico-limbic circuits, especially altered hippocampal-prefrontal (HC-PFC) connectivity repeatedly associated with impaired cognition and social skills (Baas *et al.*, 2008). Postmortem studies show that hippocampus and cortical regions are anatomically smaller in brains of patients with schizophrenia (Sugranyes *et al.*, 2015; Kalmady *et al.*, 2017; Guo *et al.*, 2018; Huang *et al.*, 2018). On the other hand, anterior hippocampus is thought to be hyperactive in patients with schizophrenia which could be explained as a compensation mechanism (via increased metabolism) for such a reduction in the gray matter volume, whilst prefrontal cortex show both increased and decreased activation (Cohen *et al.*, 1987; Cleghorn *et al.*, 1989; Malaspina *et al.*, 1999).

Dopamine hypothesis

Dopamine hypothesis is the first revolutionary hypothesis ever formulated along the biological evidence of disruption in the brain homeostasis of patients suffering from schizophrenia. This hypothesis considers a dysregulation of dopaminergic system in the brain as the main etiology of schizophrenia. In many studies throughout last four

decades there are substantial evidences observing hypodopaminergia in mesocortical neurons and hyperdopaminergia in mesolimbic neurons. The hypodopaminergia was later associated especially with striatum, which is ever since known as a centerpiece of which dysregulation is implicated in acute state of psychosis that is represented by elevated presynaptic striatal dopamine availability and DA receptor density in PET and SPECT studies (Hietala *et al.*, 1995, 1999; Howes *et al.*, 2012). The DA transmission hyperactivity is mainly seen in D2 receptors, hence all the antipsychotic drugs (the first and also the new generic ones) currently licensed decrease function of D2R in the striatum, while D1 receptors mediating the release of DA in PFC are characterized by hypofunction, which has been linked to cognitive deficits and negative symptoms. However, these drugs only work by decreasing spontaneous phasic DA release, therefore inhibiting of positive effects does not work or works only a little for cognitive impairment or negative symptoms. Nevertheless, nowadays studies agree that DA system does not act in isolation and that it rather predominantly interplays among glutamatergic system (Stone *et al.*, 2010).

Glutamate hypothesis

Accumulating evidence suggests that dysregulation in glutamatergic system plays a key role in schizophrenia shielding not only positive and negative symptoms, but also the cognitive ones. Glutamate synapses contain NMDA (N-methyl-D-aspartate) receptors that are thought to be hypofunctioning throughout the schizophrenia patients. Animal models studying psychosis like symptoms triggered by NMDAR hypofunction administrate NMDAR antagonists such as PCP or ketamine and are currently used to describe specific schizophrenia circuits (Jodo *et al.*, 2005; Jeevakumar *et al.*, 2015; Zurawek *et al.*, 2018). NMDAR antagonists increase glutamate release on some synapses via stimulation of AMPA receptors which leads to cortex overexcitation, especially in the dorsolateral PFC and consecutive disorganization and pathological activity (Tsukada *et al.*, 2005; Pezze *et al.*, 2014).

Animal Models of Schizophrenia - an Overview

Since there is a bigger awareness of homology amidst the brain regions of primates and rodents, many types of animal models are used to simulate schizophrenia-like symptoms in rodents allowing us to better understand the underlying schizophrenia neurobiology in humans and eventually to test a new therapeutic targets.

Oligodendrocyte-related Environmental Animal Models of Schizophrenia

Cuprizone-fed mice/rats model

Cuprizone is a copper chelator that is highly toxic in certain dosage. However, lower doses are not fatal to mice and the main perturbation consists of the consistent demyelination and loss of oligodendrocytes, therefore this new model is used as a simulation of these alteration in the schizophrenia-related pathophysiology (Gregg *et al.*, 2009; Makinodan *et al.*, 2009; Yang *et al.*, 2009).

Oligodendrocyte-related Genetic Animal Models of Schizophrenia

Plp1 transgenic mice model

The first animal study showing the abnormalities in the ultrastructure of the myelin sheath using a transgenic mice carrying an altered *plp* gene (deletion within exon III), a major integral membrane protein, successfully mimicked schizophrenia-like behavior changes (Boison and Stoffel, 1994). Studies using the same animal model partly replicated the same results (Tanaka *et al.*, 2009).

Perturbing NGR1/erbB4 signaling animal model

Studies using genetic animal model with a knockout of NRG1 or its tyrosin-kinase receptor erbB4 that are suspected to play a huge role in a neurodevelopmental neural migration suggest that these genes are at high risk considering the schizophrenia. Mutant mice carrying either NGR1, or erbB4 deletion report schizophrenia-like cognitive deficits and social behavior alterations (O'Tuathaigh *et al.*, 2007).

More interestingly the hypomorphism of these genes results in the decreased function of NMDA receptors validating the glutamate hypothesis of schizophrenia mentioned above.

Microglia-related Environmental Animal Model of Schizophrenia

LPS-exposed infant model

Higher levels of IL-1α, IL-1β and/or TNF during brain development may play a critical role in the onset of schizophrenia, namely infants with elevated proinflammatory cytokine levels report WM damage which, as mentioned before, gives rise to schizophrenia-like symptoms (Favrais *et al.*, 2011). This might be evolving from oligodendrocyte apoptosis in the presence of microglia (Takahashi *et al.*, 2003). To investigate the possible negative effect of the inflammation, there has been used an animal model applying lipopolysaccharide (LPS) infusion into the yet undeveloped fetal rodent brain (Burd *et al.*, 2010). In this model, the putative role of LPS as a Toll-like receptor 4 (TLR4) specific agonist is its activation that results in microglial TNF and interleukin proinflammatory release (Taylor *et al.*, 2010).

Poly I:C-exposed maternal model

Poly I:C model is another animal model that emphasizes the factor of maternal infection during gestational days and its pathological effect to the neurodevelopment of the offspring. In this model, pregnant rodent female are treated with polyinosinic-polycitidilic acid (Poly I:C) since it is known that this acid can mimic a viral infection in the course of the pregnancy via activation of Toll-like receptor 3 (TLR3) pathway (Zuckerman and Weiner, 2005; Ozawa *et al.*, 2006; Wolff and Bilkey, 2008).

Astrocyte-related Environmental Animal Model of Schizophrenia

Kynurenic acid-increased level model

KYNA environmental animal model is tasked in examining the impact of kynurenic acid (KYNA) in the development of schizophrenia-like symptoms. This animal model assumes that increased levels of KYNA in the nervous system of rodent, eventually humans, inhibits NMDA receptors and in accordance to hyperglutamate hypothesis of schizophrenia, overexcitation and subsequent disorganization of neural activity (especially in the dorsolateral mPFC) causes psychoses symptoms and cognitive deficits. KYNA is a metabolite produced by certain types of astrocytes, therefore this model is admitted as a result of astrocyte dysregulation (Chess and Bucci, 2006; Chess *et al.*, 2007; Chess, Landers and Bucci, 2009).

L-AA-exposed model

In this environmental animal model, rodents are injected with L-α-aminoadipate (L-AA), a specific astrocyte toxin. These animals with a significant loss of astrocytes report cognitive impairment (affected attentional set-shifting, working memory, reversal learning function) suggesting the role of astrocytes in the normal cognitive function of the brain (Lima *et al.*, 2014).

Lactate transport-disrupted model

Animals trained for long-term memory tasks need higher levels of extracellular lactate (byproduct of glycogen metabolism), which is a dominant energy source for neurons suggesting an existence of astrocyte-neuron coupling. Astrocytes, but not neurons, store glycogen. Disrupted expression of the astrocytic lactate transporters monocarboxylate transporter 4 (MCT4) or MCT1 ends up with animals showing cognitive deficits because of the disruption of glycogen breakdown and lactate release. In this model, to test if astrocytic glycogenesis affects cognitive function, animals are injected with inhibitor of glycogen phosphorylation 1-4-dideoxy-1,4-imino-D-arabinitol (DAB) (Suzuki *et al.*, 2011).

Astrocyte-related Genetic Animal Models of Schizophrenia

Serine racemase knockout mice model

D-serine is an important co-agonist of the NMDA receptor at glycine site as it is known that glutamate by itself is not enough for NMDAR activation. However, serine binds itself to NMDAR only as a D-isomer, but not L-isomer. Because of it, astrocytes need an enzyme called serine racemase that is capable of this conversion. Animal models that selectively perturb the function of astrocytic genes encoding for serine racemase can facilitate us better understanding of schizophrenia-like symptoms (Balu *et al.*, 2013).

Interneurons-related Environmental Animal Models of Schizophrenia

MAM acetate-exposed rats model

MAM model is based on administration of methylazoxymethanol (MAM) acetate at gestational day 17 to the pregnant rats or other rodents. These animals subsequently show behavioral deficits such as impairment of prepulse inhibition of the startle response, deficits in learning and memory and eventually social deficits. The analysis of these rats shows anatomical alteration such as loss of parvalbumin interneurons (Hradetzky *et al.*, 2012; Snyder, Adelman and Gao, 2013; O'Reilly, Perica and Fenton, 2016; Gulchina *et al.*, 2017).

Neonatal ventral hippocampal lesion model

Neonatal ventral hippocampus lesion (NVHL) model is a neurodevelopmental animal model investigating the role of hippocampus – prefrontal cortex and hippocampus – nucleus accumbens efferent pathways in the etiology of schizophrenia. Early

excitotoxic damaged rats with NVHL report cognitive deficits such as spatial memory impairment (Brady, Saul and Wiest, 2010) or extra-dimensional shift disruption (Marquis, Goulet and Doré, 2008) as adults. Disturbed behavior of adult rats resulting from PFC pyramidal neurons affected by NVHL seems to be interconnected among various neurotransmitter systems. Stimulation of VTA in the NVHL rats led to an increase in firing of pyramidal neurons in PFC instead of characteristic decrease. This DA modulation of cortical interneurons might be a result of an altered maturation of local PFC inhibitory circuits in NVHL rats during brain development. Indeed, NVHL not only disrupt hippocampal-dependent spatial memory (measured in the radial arm maze), but more importantly, the PFC interneurons lack the function of local inhibition (Tseng *et al.*, 2008).

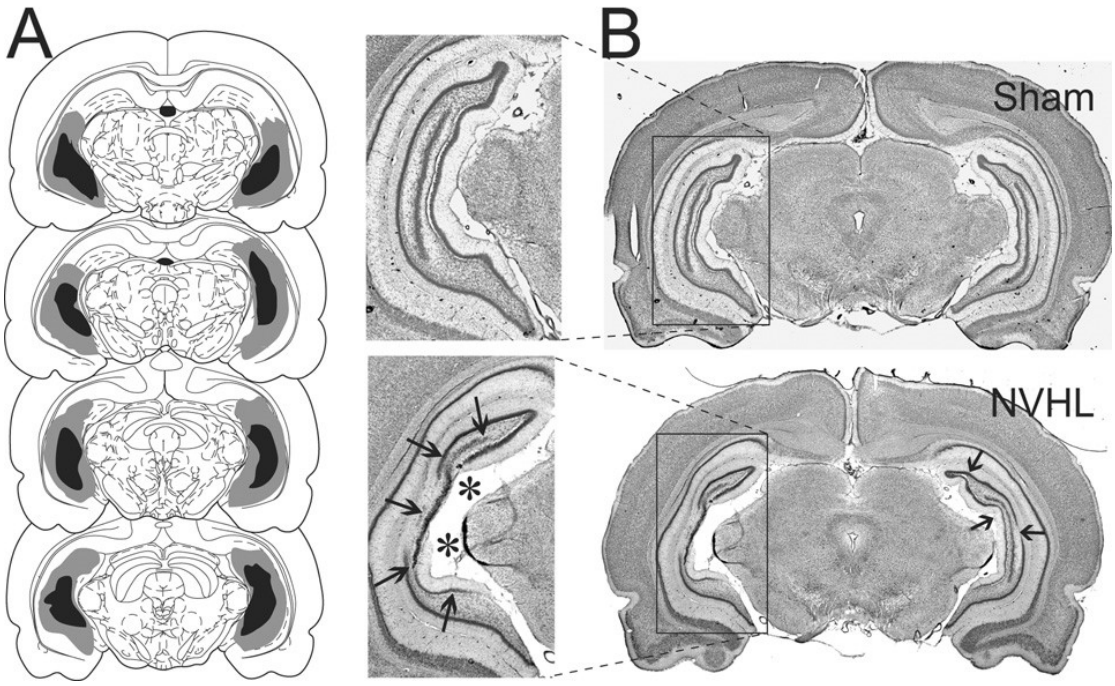

*Figure 1**: Neonatal ventral hippocampal lesion**: A: Gray and dark areas indicate maximal and minimal extent of damage, respectively. B: Coronal Nissl stained sections showing the ventral hippocampus of a sham rat (top) and a typical NVHL (bottom) with cell loss (Tseng et al., 2008)*

Physiological Neuron-glia Communication

The whole nervous system and its functional and structural integrity depends not only on the appropriate function of glia and neurons by themselves, there rather need to be provided a tactful two-way communication among several types of cells. Neuron-glia bidirectional interactions are involved in phenomena like synaptic activity, conduction of action potential, neuronal growth, neuronal regeneration or neuronal immune protection.

Neuron-oligodendrocyte Interactions (Myelin Biogenesis)

Rapid and controlled neural impulse conduction depends on the synthesis of myelin sheath around axons. Myelin fibrils are produced by specialized glia cells, such as oligodendrocytes in CNS or Schwann cells in PNS. The function of myelin sheath is not only in maximizing the speed of conduction of action potentials, but also ensuring simultaneous arrival of impulses from various brain regions that need to be coordinated.

It is known that there is a close association between impulse activity of neurons and myelination of their axons. Intense research has been settled with the aim at delineating the neuron-glia signaling involved in this process. However, it seems that the neuronal activity-induced myelination is only working in the CNS, while the mechanism in the PNS seems to be different as much as oligodendrocytes do not need the presence of neurons to initiate a myelination (Rome *et al.*, 1986), whilst Schwann cells necessarily require a contact with axon (Dong *et al.*, 1995).

In the case of optic nerve, a blind mole-rat has naturally smaller number of myelinated axons surrounded with a thicker sheath (Omlin, 1997), while accelerated myelination in rabbit optic nerves is seen after artificial stimulation of rabbit's eyes (Tauber, Waehneldt and Neuhoff, 1980). Another study (Lubetzki *et al.*, 1993) suggests the neuron activity-dependent myelination. In the culture, neuronal cell bodies affected by TTX (sodium channel blocker which blocks action potential activity) showed decreased myelination by about 85 % and neither the number of neurons nor the number of oligodendrocytes were changed after the TTX treatment. Furthermore, increased myelination without significant effect on the number of oligodendrocytes or neurons, has been shown after stimulation of neuronal activity (duration and frequency of spontaneous action potentials) by sodium channel activator α-scorpion toxin (α-ScTX) in the developing neurons suggesting the role of

down-regulation in the neuroplasticity by sodium influx (Dargent and Couraud, 1990).

First in the brain development, there is a crucial period when oligodendrocyte precursor cells (OPCs) migrate to a final target (axon) and when they reach the point, they stop migrating and start differentiating into oligodendrocytes. Then the extrinsic signals from neurons became a critical in the way of controlling the proper timing during the differentiation alone and the amount of oligodendrocytes around one axon that is required in myelination. One of the factors produced by neurons (and also astrocytes) regulating the proliferation and survival of oligodendrocytes is Platelet-derived growth factor (Richardson *et al.*, 1988). Another neuron-derived molecule regulating the survival of myelin-forming cells is neuregulin (NRG) whose epidermal growth factor (EGF)-like motif binds and subsequently activates membrane receptors such as ErbB2, ErbB3 or ErbB4 (with tyrosine kinase activity) on oligodendrocytes. Oligodendrocytes can't undergo the process of differentiation in the absence of these receptors and their function of ensheathing the axons fails to be completed (Canoll *et al.*, 1996; Marei *et al.*, 2013).

Seventy percent of total dry weight of myelin is lipids. Neuronal-induced changes in the lipid organization consist of myelin basic protein-dependent (MBP acts as a lipid coupler thanks to the highly positive charge) lipid condensation of the oligodendroglial membrane (Fitzner *et al.*, 2006). What more, reduced MBP mRNA was found in the subjects with schizophrenia (Matthews, Eastwood and Harrison, 2012).

Another pro-myelination molecule is Adenosine and similarly, its secretion is activated as a result of impulse stimulation (Stevens *et al.*, 2002).

Neuron-microglia Interactions

Screening of the bi-directional interaction between neurons and microglia is an essential step toward understanding of the neurodegenerative disorders. Microglia with the monocyte-macrophage cell origin are commonly seen around degenerating neurons where they produce both neurotoxic and neuroprotective factors influencing either neuroinflammation or regeneration and degeneration processes. However, even though it is commonly known how microglia work after a brain insult, the role of microglia in an uninjured brain remains somehow unclear.

Considerable evidence suggests that cytokines and other molecules produced by immune system cells can shape a development of CNS itself (Urakubo *et al.*, 2001;

Meyer *et al.*, 2006). Early postnataly in the critical developmental period, there need to be formed much more synaptic connections than it is needed in the adult brain system. With respect to the neurodevelopmental hypothesis of the origin of neuropsychiatric disorders, when the inner synaptic developmental program does not work properly, there is a possibility of developing a neurological aberration in one's future. Microglia also play it's own role in an activity-dependent synaptic pruning. The synaptic pruning comprises of reduction of some synapses, so the other ones can be maintained and strengthened – that is when the great number of synapses is extensively reduced. A candidate mechanism in the pruning of synapses via microglia might be a complement cascade (C1q: the initiating protein of complement cascade is localized to synapses) or classical phagocytosis (Stevens *et al.*, 2007; Schafer *et al.*, 2012).

The connecter in the neuron-microglia interaction would be probably kynurenic acid (KYNA), which is a tryptophan metabolite produced in the increased levels during infection by microglia. KYNA has an influence on the basal neurotransmitter levels. Dopamine neurons are especially sensitive towards KYNA. DA neurons under the stimulation of KYNA happen to be in the intense firing, especially in globus pallidus, prefrontal cortex and nucleus accumbens. The mechanism seems to work via antagonizing of NMDA receptors by KYNA and subsequent glutamate hyperfunction underlying the glutamate hypothesis of schizophrenia (Olsson *et al.*, 2009; Winter *et al.*, 2009).

Neuron-astrocyte Interactions

One of the astrocytic functions consists of the regulation of synapse formation and its appropriate function and subsequent mediating of neuroplasticity. Astrocytes promote synaptogenesis through expression of cell adhesion and matricellular molecules. Cell adhesion molecules (CAMs) work as a stabilizer of axo-dendritic contact. CAMs support synaptic function in different ways – one of them is dependent on scaffold mechanisms that align pre- and postsynaptic sites, another one is for example an expression of axon guidance molecules, whose function subsequently affect the cytoskeleton of growth cones (Garrett and Weiner, 2009).

Communication via gap junctions enables astroglial network to form a large plastic ensembles (Ma *et al.*, 2016; Clasadonte *et al.*, 2017), which can also be affected by neurotransmitters produced by neurons suggesting the regulation of astrocytes by neuronal activity (Fróes *et al.*, 1999). Although the mechanism is not properly

understood yet, studies suggest that the neuron depolarizing activity of K+ increases GJ coupling (De Pina-Benabou *et al.*, 2001).

Astrocytes metabolize lactate (a main source of energy used by neurons) from glucose. It has been proposed that selective delivery of glucose or its metabolite lactose into the astroglial network decreases the depression of synaptic transmission resulting from the extracellular glucose deprivation. Hence, the data suggest that astrocytes directly contribute to the metabolism of neurons. The supply is provided by an activity-dependent intercellular pathway, which facilitates delivery of glucose from blood vessels to neurons (Suzuki *et al.*, 2011).

Astroglia with its gap junctions and especially calcium ion signaling (whose responses encode neuronal information) have been proposed to play an important role in the long term potentiate and long term depression. This astrocytic role in the synaptic plasticity (regarding learning and memory) has been recently better understood. Regulation of neural network activity is probably critical in the region of hippocampus. This suggests that not only neurons can influence a morphological and physiological plasticity of astrocytes, but also astrocytes can significantly influence the neural activity via depolarization or hyperpolarization of neurons (Fellin *et al.*, 2004; Henneberger *et al.*, 2010; Chen *et al.*, 2012; Navarrete *et al.*, 2012; Szabó *et al.*, 2017). Also, the glutamate uptake by astrocytes keeps extracellular glutamate levels decreased due to the protection of neurons against glutamate-induced neurotoxicity (Takano *et al.*, 2018).

Dysfunction of Neurons in Schizophrenia

Neurons are main cells in the nervous system carrying and transmitting information within the synapses to other nerve cells, muscle, or gland cells. Their interconnected regions form a functional and structural complex. This complex seems to be disrupted in schizophrenia. In the following chapter, I present some examples.

Principal Neurons

Principal neurons are cells that generate and direct action potential via their long axons and constitute more or less complex neuronal patterns that serve to the controlled transference of neural information. One of the major hypotheses explaining the etiology of schizophrenia operates with a dysfunction of principal neurons with dopamine synaptic activity. DA neurons dysfunction is a result of imbalance between the deficits in function of cortical DA neurons manifesting as hypodopaminergia and excess of subcortical neurons function that manifests as hyperdopaminergia (Nakao, 2017; Nakao *et al.*, 2019).

Through disrupted synchronous oscillatory firing (especially in the gamma frequency band: 30-100 Hz) of pyramidal neuronal networks in the cerebral cortex are mediated cognitive deficits and other schizophrenic symptoms. Decreased density of pyramidal dendritic spines (Garey *et al.*, 1998) and decreased average of pyramidal somal area (Sweet *et al.*, 2003) (integrated in the long-range associational as well as local intrinsic cortico-cortical connections) is seen in postmortem schizophrenic patients. What more, analyses of molecular profiles reveal altered mRNA expressions, whose products have function in synaptic plasticity and other pyramidal mechanisms in schizophrenia (Pietersen *et al.*, 2014). Also, the loss of microRNAs in pyramidal neurons can lead to the subsequent deficit in prefrontal parvalbumin positive interneurons resulting in an altered inhibitory transmission (Hsu *et al.*, 2012). Disruption in the pyramidal cells layer 3, especially in DLPFC in which more likely leads to an altered development of transcripts regulating dendritic spines, also leads to certain cognitive deficits in monkeys (Dienel, Bazmi and Lewis, 2017).

NMDA receptor antagonists have different effect on principal (pyramidal) neurons and interneurons. Indeed, in awaken rats NMDAR antagonists increase the firing rate of the majority of pyramidal neurons, while activity of GABA interneurons remains decreased. The cortical overexcitation of pyramidal neurons, which is not properly regulated by interneurons, causes schizophrenia-like phenotype in animal models (Homayoun and Moghaddam, 2007).

Recent study by Leitman et al. suggests a direct role of impaired NMDAR signaling on pyramidal neurons at gamma band oscillations in cognitive performance (Tatard-Leitman *et al.*, 2015). And it was demonstrated that a chronic NMDAR antagonism increases binding of DA onto the D1 receptor in PFC, while the level of extracellular DA remains decreased in the same region of cortex. The afflicted monkeys subsequently display impairment in working memory performance (Tsukada *et al.*, 2005). The above mentioned studies by Leitman et al. and Tsukada et al. in which NMDAR antagonism is induced on the pyramidal neurons and then the cognitive deficits are observed support the hypothesis that parvalbumin interneurons NMDAR antagonism (which will be discussed in the next chapter) is not the only mechanism that results in decrease of PFC DA levels and increase of subcortical DA levels. Pyramidal neurons are also affected by NMDAR antagonism.

Interneurons

Interneurons morphologically differentiate from other types of neurons (the principal ones) in the mechanism of connection, which consist only of one single area targeted via axon and dendrites. Interneurons have an inhibitory function and are crucial for stabilizing the excitatory/inhibitory balance and subsequent neuronal synchronization. Interneurons release GABA, which results in hyperpolarization of targeted cell.

One of the most common features in patients suffering from schizophrenia is alteration in GABA-related markers in the frontal lobes, as well as amygdala and hippocampus. These alterations consist of reduced gene expression for glutamic acid decarboxylase-67, an enzyme important for synthesis of GABA itself (Hashimoto *et al.*, 2008; Franois *et al.*, 2009).

Currently deeply studied type of interneurons in the field of schizophrenia is parvalbumin interneurons. They connect via inhibitory synapses onto the either pyramidal axon initial segment (parvalbumin-expressing chandelier cells) or the neuron body (parvalbumin-expressing basket cells). Parvalbumin interneurons are characterized by the fast-spiking phenotype and expression of the calcium-binding protein parvalbumin. Their function provides appropriate generating of cortical oscillation in the gamma range (30-120 Hz), which is mediated by synchronization in feedback and feedforward inhibition of principal (especially pyramidal) neuron cells complex. Gamma oscillations are presumably critical in enhancing information processing (Cardin *et al.*, 2009; Sohal *et al.*, 2009). Moreover, huge evidence supports the idea that impairment in working memory, attention and other cognitive

aspects results from disturbed oscillatory activity especially of gamma-band responses in the PFC (Senkowski and Gallinat, 2015).

Based on the study by Steullet et al., animals carrying genetic and/or environmental risks relevant to schizophrenia (and other neuropsychiatric disorders) show deficits in PVI accompanied by oxidative stress (Steullet *et al.*, 2017). What more, imbalance between the amount of antioxidants and reactive oxygen species (ROS) and eventually reactive nitrogen species (RNS) can lead to an abnormal cell proliferation/differentiation, damaged energy metabolism and neurotransmission (Ishikawa *et al.*, 2008). Hence, antioxidants/redox regulators could be a new potential interest among research of schizophrenia pathology.

Cumulating evidence suggest that some of the symptoms in schizophrenia are constituted by an imbalance between glutamatergic excitation and PVI GABAergic inhibition. The mechanism by which increasing of the firing rate of pyramidal cells after the decreasing of the inhibiting activity of putative GABA interneurons drives an altered cortical connectivity and possible cognitive impairment works via NMDA hypofunction. Thus, hypothesis focusing on interneuron NMDA receptors expect the hypofunction of NMDAR as a diminishing effect of the inhibitory control of PFC output neurons (Homayoun and Moghaddam, 2007). NMDAR antagonists can bind to all NMDA receptors, but the effect will mostly be distinguishable on those being active, and because GABA interneurons are continuously depolarized and exhibit intensive firing levels, the NMDA antagonists are likely to affect them first (unlike pyramidal cells that do not continuously fire nor depolarize themselves) (Tseng and O'Donnell, 2006).

In the development of child neuronal system, there is a critical point during postnatal period in which cortical network plasticity need to be stabilized by the maturation of PVI and to them associated extracellular matrix (Lee *et al.*, 2006).

Consistently with the neurodevelopmental hypothesis of schizophrenia, decreased density of functional parvalbumin interneurons, especially in mPFC and hippocampus, or their altered functions are found in offspring prenataly administrated with antimitotic methylazoxymethanol (MAM) acetate, which produces disruption of brain development (Lodge, Behrens and Grace, 2009; Hradetzky *et al.*, 2012; Snyder, Adelman and Gao, 2013). And at the same time, exposure to MAM results in the development of NMDAR hypofunction. Also, the molecular basis of its dysfunction might be a feature of epigenetic hyper-repression of the Grin2b promoter and subsequent reduced expression of NR2B, a NMDAR

subunit (Gulchina *et al.*, 2017). It seems to be important to mention association between PFC and amygdala. Speaking of anxiety-like behavior in the animals exposed to MAM gestationally, these animals show and abnormal activities of amygdala (which is known as a brain center of anxiety) during puberty and heightened anxiety which can be stabilized by diazepam, an antianxiety drug (Du and Anthony A Grace, 2016; Du and Anthony A. Grace, 2016).

Another neurodevelopmental model mimicking schizophrenia symptoms settled in the offspring early postnataly is a neonatal lesion in ventral hippocampus (NVHL) model (Franois *et al.*, 2009). Ventral hippocampus is closely associated with mPFC via efferent pathway, therefore lesion in ventral hippocampus affect behavioral output that depends on the function of mPFC such as set-shifting. Furthermore, NVHL not only cause an altered dendritic spine density of pyramidal neurons in mPFC and nucleus accumbens (Flores *et al.*, 2005; Marquis, Goulet and Doré, 2008), but also disrupt extra-dimensional shift as an analogy of cognitive flexibility in rats and other rodents, although reversal learning remains to be significantly unchanged (Marquis, Goulet and Doré, 2008; Placek *et al.*, 2013). Another cognitive deficit in NVHL rats is also spatial working memory impairment (Brady, Saul and Wiest, 2010).

Another models of schizophrenia reveal genetic predisposition for the loss of interneurons function and subsequent pathological behavior under an altered gene expression. It was found that genes associated with risk for schizophrenia are important for the normal development of cortical interneurons (especially parvalbumin positive) suggesting that schizophrenia is a disorder with a strong genetic component. For example variation in neuregulin 1 (NRG1) and its receptor ErbB4 leads to an altered development of inhibitory circuits in the cortex via cell-autonomous regulating of the connectivity of specific GABA interneurons. In particular, ErbB4 is expressed not only by the pyramidal neurons, but also many parvalbumin-expressing chandelier and basket cells, which were mentioned above (Fisahn *et al.*, 2009; Fazzari *et al.*, 2010; Wen *et al.*, 2010; Ting *et al.*, 2011).

Common observation in many schizophrenia models is a loss of interneurons (especially parvalbumin positive) and their altered function that after all mediate disinhibition of cortex. This feature is in the center of many new therapeutic approaches through which should be manipulated with the function and number of these stabilizing cells.

Dysfunctions of Glia in Schizophrenia

Glia are the non-neuron cells in the nervous system. They provide many functions that can not be maintained by neurons such as myelin forming, support and protection of neurons or regulation of homeostasis. Thus, the function of neurons to the some point depends on function of glia cells.

Oligondendrocytes and Oligodendrocyte-precursor Cells

Oligodendrocytes are thought to play an important role within the neural connectivity system as long as it is known that this type of glia cells is critical for the appropriate synthesis of the myelin sheath. The level of cognitive performance is dependent on the quality of the communication between the brain regions, hence, the origin of the myelination process itself is an evolutionary upset once formed to keep pace with a complex behavior associated with higher animals, specifically vertebrates.

Many studies (Uranova *et al.*, 2001, 2011; Schmitt *et al.*, 2009) reveal that neocortical regions (PFC and Hippocampus) are affected by a significant decrease in the number of oligodendrocytes. The loss is specifically noticeable in the posterior area: left and right CA4 regions and anterior area: left CA4 of hippocampus, therefore researchers suggest and substantial evidences agree on the altered formation of myelin in patients with schizophrenia (Bartzokis *et al.*, 2003).

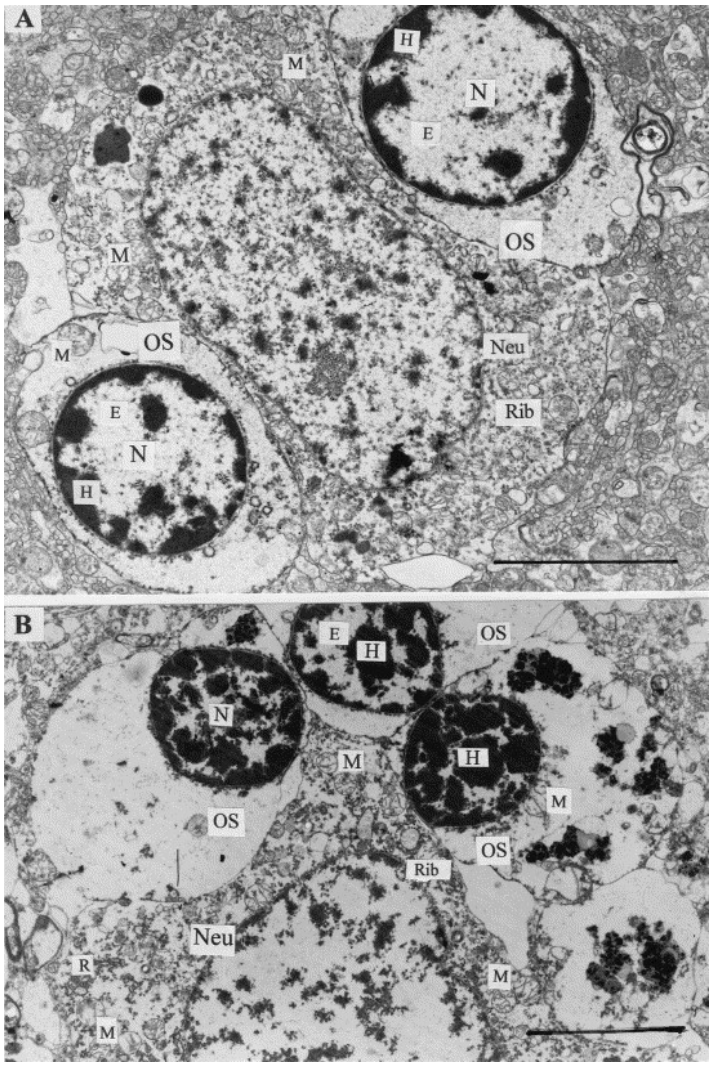

Figure 2: Oligodendroglial satellites (OS) of neuron (Neu) in the prefrontal cortex in control brain (A) and reactive changes of OS of Neu in PFC in schizophrenic brain (B) (Uranova et al., 2001)

The decreased myelination is hypothesized to cohere with some symptoms of schizophrenia, especially the cognitive deficits. The

alteration of myelination was also observed in studies using diffusion tensor imaging (DTI) pointing to an abnormal white matter microstructural organization indicated by reduced fractional anisotropy primarily in corpus callosum, anterior cingulate, left frontal and temporal regions (Phillips *et al.*, 2009; Whitford *et al.*, 2010; Camchong *et al.*, 2011; Holleran *et al.*, 2014).

Gene ontology study (Katsel, Davis and Haroutunian, 2005) has reported altered transcripts encoding for myelin-related proteins which are responsible for glial differentiation or myelin synthesis critical generally in the formation and integrity of axon-myelin interaction. One of the best known genes suspected in the pathology of schizophrenia is for example Neuregulin-1 (NRG1) which is responsible for neural migration involved in myelination during the brain development and whose unappropriated expression is reported in schizophrenia patients (Wang *et al.*, 2009).

As far as oligodendrocyte-precursor cells are considered, the researches using immunoreactive markers OLIG1 and OLIG2 typifying the presence of oligodendrocytes themselves highlight a significant decrease in the density of these precursors suggesting the link in an altered myelination in schizophrenia (Georgieva *et al.*, 2006; Mauney *et al.*, 2015).

Astrocytes

Astrocytes have the greatest representation, meaning the quantity, in the CNS among the two other types of glia cells (microglia, oligodendrocytes). Astrocytes are thought to be involved in a vital mechanism for an appropriate function of neurons since astrocytes play an indispensable role in homeostatic changes and cellular cross-talk. The mechanism by which astrocytes have an impact on neuron function is for example expressing neurotransmitter receptors, mediating a neuronal metabolic activity, synthesis of substrate lactate which is preferred as a neuronal source of energy among the other sources or clearance of neurotransmitters (Lima *et al.*, 2014). Due to the dynamic neuron-astrocyte interactions, the pathology of astrocytes have been widely studied in the past few decades in the field of neuropsychiatry as it is expected the behavioral output of the changes in neuron-astrocyte network integrity. In the recent study by Lee and collective it was found that transgenic mice with a selective expression of tetanus neurotoxin (TeNT) in astrocytes show an impaired behavior in the novel object recognition test that comes as a result from an altered gamma frequency range and is restored by suppression of TeNT expression (Lee *et al.*, 2014).

Increased brain levels of the kynurenic acid (KYNA) were found in the cerebrospinal fluid of schizophrenia patients. KYNA is an endogenous TRP metabolite that antagonizes NMDA and α7 nicotinic receptors and is produced by certain type of astrocytes. And as mentioned before, inhibiting of the function of NMDA receptor results in schizophrenia-like symptoms (Linderholm *et al.*, 2012). In addition, animal studies in which researchers elevate the concentration of KYNA in rodents show damaged condition responding (Chess and Bucci, 2006; Chess, Landers and Bucci, 2009) and spatial working memory deficits (Chess *et al.*, 2007) suggesting the role of astrocyte pathology in the cognitive impairment.

Plenty of animal models have been done for a purpose of modulating an astrocyte pathophysiology in the brain. A wide range of astrocytes function is in need to be studied due to a considerable number of homeostatic mechanisms astrocytes are involved in. For example, in one of the model, animals are injected with a specific astrocyte toxin L-α-aminoadipate (L-AA) in the mPFC followed-up by histological analysis of mPFC that reveals significant loss of astrocytes. Injected animals report affected attentional set-shifting, working memory and reversal learning. More interestingly, astrocyte damage leads to a neuronal loss and eventually dendritic atrophy in the mPFC and it is thought to be responsible for the cognitive impairment showed in the behavioral analysis of injected animals (Lima *et al.*, 2014).

As mentioned before, one of the important functions of astrocytes is a regulation of the energetic metabolism in neurons. Astrocytes can utilize glycogen as a source in glucose metabolism. While animals or humans are trained for example in a long-term memory task, astrocytes supply neurons with lactose, an energy substrate. Disruption of the astrocytic lactate transporters has the result of amnesia and generally impaired LTP, but not the impairment of short-term memory formation. These results suggest that altered astrocyte-neuron transport of lactate can produce cognitive impairment similar to the one in schizophrenic patients and that the glycogenolysis (in which astrocytes play an indispensible role) is important mechanism in the term of neuroplasticity (Suzuki *et al.*, 2011).

Astrocytes are also needed in the regulation of the glutamate synaptic transmission. In accordance with the glutamate hypothesis of schizophrenia, the hypertransmission of glutamate leads to the development of schizophrenia-like symptoms. Rats treated with ceftriaxone, an antibiotic that induces GLT-1 up regulation by selective enhancing, happened to report impairment in the PPI of the acoustic startle reflex (Matute *et al.*, 2005; Bellesi *et al.*, 2009).

Serin racemase play a role in converting L-serine into D-serine, which is a functional isomer co-activating the NMDAR at the glycine site. Although the predominant producers of this enzyme are neurons, a considerable quantum is also produced by astrocytes and thus, disruption of glia cells leads to defect in the expression of this important co-agonist molecule. Transgenic rats which lack the D-serine, displayed cognitive abnormalities as well as morphological and neurochemical consistent with those observed in NMDAR hypofunction-induced schizophrenic animals (Balu *et al.*, 2013).

Another function of astrocytes is a secretion of trophic factors and extracellular matrix (ECM) proteins. These proteins including for example proteoglycans support growth of neurons or appropriate synaptic activity. These factors are important during the development for establishing of the neural networks in an organized manner, which neuronal plasticity is dependent on. We can ensue from the function of neurotrophic factor such as BDNF (which is produced by astrocytes), that a distortion of its function ends-up with an animal afflicted by cognitive deficits (Cohen-Cory *et al.*, 2010). While overexpression of BDNF in hippocampus has an anxiolytic and also antidepressant-like effect, therefore increase in the synthesis of this factor has a strong therapeutic potential (Quesseveur *et al.*, 2013).

Emerging need for investigation of astrocytes and other glia cells in schizophrenia and other neuropsychiatric disorders is highlighted because of the limitations of currently used pharmacotherapy, which is mainly pointed to the manipulations of neurons themselves, whereas astrocyte pharmacotherapy promises a new operational targets with possibly less negative side effects.

Microglia

Microglia are the essential immune-related cells efficient in the brain phagocytosis, thus they play an indispensible role in the brain inflammatory processes. Microglia are the first-line defense cells in the brain comprising about 15 % of the CNS cells. Multiple lines of evidence concur with the immune-related abnormalities in schizophrenia. In particular, it was pointed out that the level of cytokines - signaling molecules has been repeatedly found increased in the brain of schizophrenic patients. What else, cytokines are released as the result of the microglia stimulation. The cytokine imbalance might lead to the consecutive development of the neuropsychiatric disorder due to the impaired structural and functional integrity of a shaping brain in the childhood (Marx *et al.*, 2001).

In the researches in which animal maternal immune system is stimulated by the injection of polyinosinic-polycytidilic acid (Poly I:C) into the pregnant rats for a purpose of mimicking the anti-viral reply Mattei, D. et al. appointed to the increased volume of IL-1β and TNF-α in hippocampus. These rats demonstrated significantly impaired pre-pulse inhibition of a startle response and other behavioral abnormalities which correlate with the cognitive symptoms of the schizophrenia patients and above that this effect was restored by application of antibiotics (Mattei *et al.*, 2014, 2017). Another study (Richetto *et al.*, 2013) reports impaired working memory in mice under the similar immunological condition.

Recent trial by Xue Li et al. (Li *et al.*, 2018) aimed to study microglial activation in the hippocampus and prefrontal cortex in the offspring brain of rats exposed to Poly I:C while being pregnant. The microglial activation was highlighted via C-PK11195 micro-PET/CT accompanying by immunohistochemistry. The bigger was the activation of microglia cells, the more robust was the impairment of pre-pulse inhibition, which again suggests development of cognitive deficits under the conditions of prenatal immunological over-activation.

The mechanism by which neuro-inflammation induces schizophrenia propably leans against the neurochemical level. The animal study by Winter et al. suggests that the maternal infection during pregnancy enhances a schizophrenia-like response of offspring via increased levels of dopamine and its metabolites in the lateral globus pallidus and prefrontal cortex. Moreover, the levels of serotonin in the hippocampus, lateral globus pallidus and nucleus accumbens are decreased at the same time resulting in neurotransmitter imbalance (Winter *et al.*, 2009).

Another animal study (Olsson *et al.*, 2009) suggests that the mechanism that leads to a higher level of dopamine especially in nucleus accumbens and to more intense firing of DA neurons especially in VTA is mediated by KYNA (tryptophan metabolite) which antagonizes NMDA receptor (Notarangelo *et al.*, 2014).

The kynurenine pathway, which mediates the metabolizing of tryptophan, is seemingly disturbed in schizophrenia patients. In the case of healthy brain, astrocytes metabolize kynurenine to kynurenic acid. When microglia are activated due to the process of neuroinflammation, the cytotoxic metabolites are produced as a result of oxidative metabolism. Inhibition of mono-oxygenase (KMO) has a therapeutic effect in the preclinical models of neurological diseases, as it is known that KMO oxidatively metabolizes kynurenine to 3-hydroxykynurenine, an oxidative metabolism product (Garrison *et al.*, 2018).

Hypothesis considering the consequences of the hyperactive inflammatory system in the brain of schizophrenia patients as an underlying mechanism of their symptoms suggests that the anti-inflammatory drugs might play a key role in the treatment of this disorder which has an offset in the critical neurodevelopmental period. During this period, the neural immune system is stabilized into the functional manner (Mizoguchi *et al.*, 2008; Laan *et al.*, 2010; Müller *et al.*, 2010).

General Discussion

Dysfunction not only of neurons (principal cells and interneurons) by themselves, but also of all the single types of glia cells (microglia, oligodendrocytes, astrocytes) is registered in schizophrenia patients and animal models mimicking schizophrenia-like symptoms.

Neocortical neurons of humans has a need of greater energy metabolism and because the neocortical region involves during evolution among higher animals, more glia cells need to be established since they mediate the neuron metabolism and other stabilizing demands. Comparative studies find bigger neuron/glia ratio in prefrontal cortex (mostly involved in schizophrenia pathology) in monkeys differing from the smaller neuron/glia ratio in humans suggesting the evolution aspect in brain development and psychiatric disorders.

At first, big effort was invested in the study of neurons since their dysregulation seemed to be a key factor in schizophrenia pathology. Then, researchers found out that the neuron dysfunction was mainly associated with the dysregulation of glia cells and because it was known that glia cells have an indispensible role in appropriate function of neurons, the research of their physiological function in schizophrenia was initiated. That is where the attribute *partners in crime* came from.

As the complex knowledge of dynamic brain system evolved, schizophrenia started to be perceived not only as a pathology of neurons or glia cells by themselves, more the disorder is now recognized as a pathology among neuron-glia specific communication which manifests in the whole brain network system.

As a result of the neuron-glia altered communication some of the disrupted physiological mechanisms are observed in schizophrenia patients and animal models. In this thesis, I have delineated an altered myelin biogenesis among neuron-oligodendrocyte interaction, an altered synapse formation, energy metabolism, cellular cross-talk or long-term potentiation and depression among neuron-astrocyte interaction and last but not least an altered developmental immune activation and dysregulation of synaptic pruning among neuron-microglia cells.

The loss of oligodendrocytes and their precursor cells in PFC and hippocampus is a common pathology in schizophrenia by which the asynchronized impulse conduction might be mediated. Also, the degrading oligodendrocytes are surrounded by microglia that underlie the neuroinflammation activity. Another function of microglia is synaptic pruning during neural development of uninjured brain. The mechanism of

the pruning could be a complement cascade or phagocytosis. KYNA metabolite is a NMDAR antagonist and is extensively produced by microglia and astrocytes in the schizophrenia. Behavior analysis of rats with a significant loss of astrocytes in mPFC shows cognitive impairment. What more, neuronal loss and dendritic atrophy is also presented. With a loss of astrocytes brain system can also lack the LTP, a neuroplasticity mechanism. The brain system can also suffer from excitoxicity as the glutamate is piled up in extracellular space and is not reuptake by astrocytic GLT-1.

For a better understanding of the bidirectional communication between neuron and glia, there are also mentioned common schizophrenia alteration of every single type of neurons (principal neurons, interneurons) and glia (astrocytes, oligodendrocytes, microglia) by themselves. The animal models used in a practice of schizophrenia research are also overviewed in this thesis.

Conclusions

It seems clear that schizophrenia is a complex neuropsychiatric disorder accompanied by an altered physiological communication between nervous system cells. The neural system is very dynamic. This is why in future research, there need to be provided studies with the emphasis on the bidirectional neuron-glia communication rather then the studies of a single type of cell as a static unit.

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